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Physical activity and risk of bleeding in elderly patients taking anticoagulants

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Abstract: **BACKGROUND** Although the possibility of bleeding during anticoagulant treatment may limit patients from taking part in physical activity, the association between physical activity and anticoagulation-related bleeding is uncertain. **OBJECTIVES** To determine whether physical activity is associated with bleeding in elderly patients taking anticoagulants. **PATIENTS/METHODS** In a prospective multicenter cohort study of 988 patients aged ≥ 65 years receiving anticoagulants for venous thromboembolism, we assessed patients' self-reported physical activity level. The primary outcome was the time to a first major bleeding, defined as fatal bleeding, symptomatic bleeding in a critical site, or bleeding causing a fall in hemoglobin or leading to transfusions. The secondary outcome was the time to a first clinically-relevant non-major bleeding. We examined the association between physical activity level and time to a first bleeding using competing risk regression, accounting for death as a competing event. We adjusted for known bleeding risk factors and anticoagulation as a time-varying covariate. **RESULTS** During a mean follow-up of 22 months, patients with a low, moderate, and high physical activity level had an incidence of major bleeding of 11.6, 6.3, and 3.1 events per 100 patient-years, and an incidence of clinically relevant non-major bleeding of 14.0, 10.3, and 7.7 events per 100 patient-years, respectively. A high physical activity level was significantly associated with a lower risk of major bleeding (adjusted sub-hazard ratio 0.40, 95%-CI 0.22-0.72). There was no association between physical activity and non-major bleeding. **CONCLUSIONS** A high level of physical activity is associated with a decreased risk of major bleeding in elderly patients receiving anticoagulant therapy. This article is protected by copyright. All rights reserved.

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Physical Activity and Risk of Bleeding in Elderly Patients Taking Anticoagulants

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ABSTRACT

Background: Although the possibility of bleeding during anticoagulant treatment may limit patients from taking part in physical activity, the association between physical activity and anticoagulation-related bleeding is uncertain.

Objectives: To determine whether physical activity is associated with bleeding in elderly patients taking anticoagulants.

Patients/Methods: In a prospective multicenter cohort study of 988 patients aged ≥ 65 years receiving anticoagulants for venous thromboembolism, we assessed patients' self-reported physical activity level. The primary outcome was the time to a first major bleeding, defined as fatal bleeding, symptomatic bleeding in a critical site, or bleeding causing a fall in hemoglobin or leading to transfusions. The secondary

outcome was the time to a first clinically-relevant non-major bleeding. We examined the association between physical activity level and time to a first bleeding using competing risk regression, accounting for death as a competing event. We adjusted for known bleeding risk factors and anticoagulation as a time-varying covariate.

Results: During a mean follow-up of 22 months, patients with a low, moderate, and high physical activity level had an incidence of major bleeding of 11.6, 6.3, and 3.1 events per 100 patient-years, and an incidence of clinically relevant non-major bleeding of 14.0, 10.3, and 7.7 events per 100 patient-years, respectively. A high physical activity level was significantly associated with a lower risk of major bleeding (adjusted sub-hazard ratio 0.40, 95%-CI 0.22-0.72). There was no association between physical activity and non-major bleeding.

Conclusions: A high level of physical activity is associated with a decreased risk of major bleeding in elderly patients receiving anticoagulant therapy.

Trial Registration: <http://clinicaltrials.gov>. Identifier: NCT00973596.

Key words: anticoagulants, physical activity, hemorrhage, elderly, risk factors

INTRODUCTION

The multiple benefits of regular physical activity on morbidity and mortality are well known (1-4). Elderly persons who are physically active are less likely to have falls and fall-related severe injuries, such as fractures (5-7) but the data on the effect of physical activity on the risk of bleeding are conflicting. While studies showed that physical activity is associated with a lower risk of severe gastrointestinal hemorrhage and hemorrhagic stroke (8, 9), other studies demonstrated that vigorous physical activity is related to an increased

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risk of subarachnoid hemorrhage in adults and bleeding events in children with hemophilia (10, 11).

Limited evidence suggests that the fear of anticoagulation-related bleeding may limit patients from taking part in vigorous physical activity (12). Moreover, it has been shown that a below-average level of physical activity may be associated with excessive anticoagulation (13). A potential explanation is that physical activity decreases the anticoagulant effect by decreasing the free warfarin concentration and thus may contribute to a better stability of the response to warfarin (14, 15). However, to our knowledge, the relationship between physical activity and the risk of bleeding in patients receiving anticoagulant therapy has never been specifically examined. Therefore, we assessed the association between physical activity and bleeding in a prospective, multicenter cohort of elderly patients receiving anticoagulants for venous thromboembolism (VTE). Because elderly persons who are physically active are less likely to fall (5-7), we hypothesized that a higher level of physical activity will be associated with a lower risk of bleeding.

METHODS

Cohort sample

The study was conducted between September 2009 and April 2013 as part of the Swiss Cohort of Elderly Patients with Venous Thromboembolism (SWITCO65+), a prospective multicenter cohort study to assess long-term medical outcomes and quality of life in elderly patients with acute VTE from all five university and four high-volume non-university hospitals in Switzerland (16).

Consecutive patients aged ≥ 65 years with acute VTE were identified in the inpatient and outpatient services of all participating study sites. We defined symptomatic deep vein

thrombosis as an acute onset of leg pain or swelling in conjunction with incomplete compressibility of a venous segment on ultrasonography or an intraluminal filling defect on contrast venography (17). Because iliac veins and the inferior vena cava may be technically difficult to compress, additional diagnostic criteria for iliac and caval deep vein thrombosis also included abnormal duplex flow patterns compatible with thrombosis or an intraluminal filling defect on spiral computed tomography or magnetic resonance imaging venography (18-20). Given that compression ultrasonography has a lower likelihood ratio for distal deep vein thrombosis (21), patients with isolated distal deep vein thrombosis were eligible only if the incompressible distal vein transverse diameter was at least 5 mm (22).

Symptomatic pulmonary embolism was defined as a positive spiral computed tomography or pulmonary angiography, a high probability ventilation-perfusion scan, or proximal deep vein thrombosis documented by compression ultrasonography or contrast venography in patients with acute chest pain, new or worsening dyspnea, hemoptysis, or syncope (23, 24).

Exclusion criteria were inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow-up (i.e., terminal illness or place of living too far away from the study center), insufficient German or French speaking ability, thrombosis at a different site than lower limb, catheter-related thrombosis, or previous enrollment in the cohort.

Eligible patients were approached for informed consent to participate in the study. The study was approved by the ethics committees at each study site and written informed consent was obtained from all participants. A detailed description of the study methods has previously been published (16).

Baseline data collection

For all enrolled patients, trained study nurses prospectively collected baseline demographic information (age, gender), comorbid conditions (history of major bleeding, recent major surgery, cerebrovascular disease, cardiac disease, diabetes mellitus, hypertension, active cancer, and chronic liver and renal disease), risk of falls, laboratory findings (hemoglobin, platelets), polypharmacy (>4 drugs), concomitant antiplatelet therapy, pre-existing vitamin K antagonist therapy, and VTE-related treatment (low-molecular-weight heparin, unfractionated heparin, fondaparinux, vitamin K antagonists) using patient interviews and hospital chart review. Collected data were recorded on standardized forms.

Assessment of physical activity

To assess patients' physical activity level at baseline, we asked patients a previously established standard question ("Which of the following affirmation best matches the type and amount of physical activity you do in your life?"), with four possible answers (25). Patients who replied "I am mostly sitting or lying and I do not move a lot" or "I often walk but I avoid to climb stairs or to carry light weight (<5 kg)" were considered to have a low physical activity level. Patients who replied "I often walk and climb stairs or carry light weight (<5 kg)" and "I engage in vigorous physical activity or carry heavy weight (>5 kg)" were considered to have a moderate and high physical activity level, respectively.

Study outcomes

Our primary outcome was the time to a first major bleeding event during follow-up. Major bleeding was defined as either fatal bleeding (death that followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration) (26),

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symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin level of ≥ 20 g/l or leading to transfusion of ≥ 2 units of whole blood or red cells (27). The secondary outcome was the time to the first clinically relevant non-major bleeding, defined as a bleeding episode not meeting the definition of major bleeding but requiring a physician consultation or a visit at the emergency department. We also assessed whether bleeding occurred after a fall.

Follow-up included one telephone interview and two surveillance face-to-face evaluations during the first year of study participation and then semi-annual contacts, alternating between face-to-face evaluations (clinic visits or home visits in house-bound patients) and telephone calls as well as periodic reviews of the patient's hospital chart. During each visit/contact, study nurses interviewed patients to obtain information about the date, type, and circumstances (i.e., following a fall) of bleeding episodes, and assessed whether the patient had died. If a clinical event had occurred, this information was complemented by reviewing medical charts and interviewing patients' primary care physicians and/or family members. We also collected international normalized ratio (INR) values throughout follow-up. A committee of three blinded clinical experts adjudicated all outcomes and classified the cause of all deaths as definitely due to major bleeding or due to another cause. Final classifications were made on the basis of the full consensus of this committee.

Statistical analysis

We calculated overall incidence rates with corresponding 95% confidence intervals (CI) for a first major, clinically relevant non-major, and fall-related bleeding by physical

activity level and compared cumulative incidences using Kaplan-Meier survival analyses and the logrank test. In patients who received vitamin K antagonists within 14 days from diagnosis, we compared the percentage of time spent in a given INR range (<2.0, 2.0-3.0, >3.0) (28) across physical activity groups by an analysis of variance, excluding the first seven days of treatment.

We examined the associations between physical activity and the time to a first major, clinically relevant non-major bleeding, and fall-related bleeding using competing risk regression models according to Fine and Gray, accounting for death as a competing event (29). We accounted for non-hemorrhagic death as a competing event when analyzing major bleeding and overall death when analyzing clinically-relevant non-major bleeding. The strength of the association between the physical activity and bleeding in the Fine and Gray model is reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence of a competing risk. We adjusted for risk factors that have been previously shown to be associated with major bleedings, including age, female gender, overt pulmonary embolism, history of major bleeding, recent major surgery, cerebrovascular disease, cardiac disease, diabetes mellitus, arterial hypertension, active cancer, chronic liver disease, chronic renal disease, risk of falls, polypharmacy, anemia, low platelets, concomitant antiplatelet therapy, and periods of anticoagulation as a time-varying covariate (30-47). In the primary analysis we assumed missing values for categorical variables to be normal/absent, but tested the impact on study results by assuming missing values to be abnormal/present in a sensitivity analysis. We considered a *P* value <0.05 to be statistically significant. All analyses were done using Stata 12 (Stata Corporation, College Station, Texas).

RESULTS

Study sample

Of 1863 patients aged ≥ 65 years with venous thromboembolism, we excluded 462 patients who had at least one exclusion criterion and 398 who did not consent to participate. After the additional exclusion of 12 patients who withdrew informed consent and three patients in whom information on physical activity was not available, a study sample of 988 subjects was included in the analysis (Figure 1). Excluded patients were statistically significantly older (median 78 vs. 75 years, $P < 0.001$) and more often female (59% vs. 47%, $P < 0.001$) than analyzed patients.

Overall, 367 (37%), 310 (31%), and 311 (32%) patients had a low, moderate, and high level of physical activity, respectively. Patients with a high level of physical activity were younger, more likely to be men, and less likely to have comorbid diseases, a high risk of falls, polypharmacy, and concomitant treatment with platelet inhibitors than patients with low or moderate level of physical activity (Table 1).

Comparison of bleeding rates

After a mean \pm standard deviation follow-up period of 22 ± 11 months, 184 of 988 patients (19%) died and 118 (12%) experienced a first major bleeding, resulting in an incidence rate of 6.9 (95% CI, 5.7-8.2) major bleeds per 100 patient-years. Seventeen (14%) major bleeds were intracranial and 9 (8%) were fatal. Overall, 174 patients (18%) had a first clinically relevant non-major bleeding and 60 (6%) had a fall-related major or clinically relevant non-major bleeding, resulting in an incidence rate of 10.6 (95% CI, 9.1-12.3) and 3.4 (95% CI, 2.6-4.3) bleeds per 100 patient-years, respectively. Patients with unprovoked VTE

had an average anticoagulation duration of 16 patient-months compared to 9 patient-months for patients with provoked or cancer-related VTE.

Overall incidence rates of major and clinically relevant non-major bleeding decreased with increasing physical activity level (Table 2). Compared to patients with a low level of physical activity, patients with a high level had a lower incidence rate of major (3.1 vs. 11.6 bleeds per 100 patient-years) and clinically relevant non-major bleedings (7.7 vs. 14.0 bleeds per 100 patient-years). Patients with a high level of physical activity also had a lower rate of fall-related bleeding (2.1 bleeds per 100 patient-years) than patients with a low physical activity level (6.1 bleeds per 100 patient-years). The incidence rate of fall-related major bleeds decreased from 2.5 bleeds per 100 patient-years in patients with a low physical activity level to 0.3 events per 100 patient-years in patients with a high physical activity level ($P=0.001$). Similarly, the incidence rate of fall-related clinically relevant non-major bleeds decreased from 3.8 bleeds per 100 patient-years in patients with a low physical activity level to 1.7 events per 100 patient-years in patients with a high physical activity level ($P=0.007$). The 2-year cumulative incidence rates of major, clinically relevant non-major, and fall-related bleeding are shown in Figure 2 A-C.

The time spent in the therapeutic INR range (2.0-3.0) increased from 54% in patients with a low physical activity level to 63% in patients with a high physical activity level (Table 3). Patients with a low physical activity level spent more time in the subtherapeutic INR range (<2.0). Although the time spent in the supratherapeutic INR range (>3.0) did not vary across physical activity levels, the majority of major bleedings (68%) related to excessive anticoagulation occurred in patients with a low physical activity level.

Association between the level of physical activity and bleeding

After adjustment for multiple confounding factors, patients with a high physical activity level had a significantly lower risk (SHR 0.40, 95% CI 0.22-0.72) and patients with a moderate physical activity level had a non-significantly lower risk of major bleeding (SHR 0.72, 95% CI 0.45-1.13) than patients with a low physical activity level (Table 4). The level of physical activity was not associated with the risk of clinically relevant non-major bleeding. However, we found a positive association between the risk of falls (adjusted SHR 1.75, 95% CI 1.24-2.48), polypharmacy (adjusted SHR 1.63, 95% CI 1.12-2.37) and non-major bleeding. The results did not change when missing values were assumed to be abnormal in a sensitivity analysis.

DISCUSSION

Our results demonstrate that in elderly patients receiving anticoagulants for VTE, the incidence of major and clinically relevant non-major bleedings decreases with increasing levels of self-reported physical activity. After adjusting for potential confounders, including the competing risk for death, we found that patients with a high level of physical activity had a significantly lower risk of major bleeding than patients with a low level of physical activity and that the bleeding risk decreased with the intensity of physical activity. The level of physical activity was not associated with risk of clinically relevant non-major bleeding.

There are several potential explanations for the observed association between physical activity and major bleeding. First, patients with a high level of physical activity had a lower incidence of fall-related bleedings in our study. This finding is consistent with prior evidence demonstrating that low levels of fitness and physical inactivity are associated with falls (6) and that exercise programs reduce the risk of falling in the elderly (48). Second, patients with

increasing level of physical activity spent more time in a therapeutic INR range, indicating that physical activity may have a stabilizing effect on the response to vitamin K antagonists. In a small case series, INR values remained stable during a constant level of physical activity, decreased with increased daily activity, and increased following a reduction in physical activity (15). The authors hypothesized that increased physical activity elevates the amount of warfarin linked to serum albumin, decreases the free warfarin concentration and subsequently, decreases the INR (15). A case-control study demonstrated that in comparison with patients whose level of physical activity was above average, patients with a below-average level of physical activity had a 1.6-fold increased risk of excessive anticoagulation (13). Finally, a low level of physical activity may reflect patients' comorbid burden, an independent predictor of serious bleeding (49). Moreover, despite extensive adjustment, we cannot exclude the possibility that the association between physical activity and major bleeding is due to incomplete adjustment or unmeasured confounders rather than a direct effect of physical activity itself.

Patients taking anticoagulants may feel limited from taking part in vigorous physical activities by the fear of bleeding (12). Our results indicate that physical activity does not increase the risk of bleeding and may encourage patients to continue physical activity with all its positive effects on health and well-being.

Although patients with a higher physical activity level had a lower incidence of clinically relevant non-major bleeding, after adjustment for differences in baseline characteristics, we did not find an association between physical activity level and non-major bleeds. Only the risk of falls and polypharmacy were associated with non-major bleeding. We can only speculate why physical activity could have a protective effect on major bleeding but not on non-major bleeding. A potential explanation is that patients with a higher

physical activity level may experience fewer severe falls, hence avoiding major bleeds but only to a lesser extent, non-major bleeds.

Our findings have clinical and research implications. Given their increased risk of excessive anticoagulation and major bleeding, frail and physically inactive patients could potentially benefit from more intensive surveillance and anticoagulation monitoring (13). Further studies are needed to explore the mechanisms by which physical activity decreases the risk of major bleeding (e.g., reduced falls risk, better anticoagulation quality) and whether exercise programs have the potential to reduce the risk of bleeding in elderly patients receiving anticoagulants. The level of physical activity should also be incorporated in future bleeding risk prediction models.

Our study has several strengths. First, to our knowledge, our study is the first to examine the association between physical activity and bleeding in patients receiving anticoagulants. Second, because practically all patients with acute VTE receive anticoagulation for at least three months regardless of their bleeding risk, the potential for indication bias is low. Indication bias is a threat to the validity of anticoagulation-related bleeding studies because physicians may decide against treating patients who they perceive to be at high-risk of bleeding (50). Finally, because our sample included elderly, multimorbid patients who were at risk of dying from non-hemorrhagic causes before experiencing a bleeding event, we used competing risk regression to account for the competing risk of death (29).

Our study has several potential limitations. First, the study sample may not reflect the full prognostic spectrum of patients with VTE because analyzed patients were younger and more likely to be men than excluded patients. Thus, we cannot rule out the possibility that the association between physical activity and bleeding would have been different in more

severely ill patients. Second, given that our cohort included patients with VTE only, our results may not be generalizable to other indications for anticoagulant treatment. Third, physical activity was only assessed at the beginning of the study and may have changed over time. Finally, we could only detect associations, not causality. Thus, we could not determine whether the level of physical activity has a direct causal effect on major bleeding or if it is simply a marker of comorbidity.

In conclusion, in this prospective multicenter cohort of elderly patients receiving anticoagulant treatment, a high level of physical activity was associated with a lower risk of major bleeding. Future studies should examine the mechanisms by which physical activity decreases the risk of bleeding and whether implementation of training programs aimed to increase physical activity decrease the risk of bleeding in such patients.

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FIGURE LEGENDS

Figure 1

Patients flow chart.

Figure 2

Panel A. Kaplan-Meier estimates of a first major bleeding by physical activity level

The 2-year cumulative incidence of a first major bleeding was 18.8%, 11.4%, and 6.2% for patients with a low, moderate, and high physical activity level, respectively ($P<0.001$ by the logrank test).

Panel B. Kaplan-Meier estimates of a first clinically relevant non-major bleeding by physical activity level

The 2-year cumulative incidence of a first clinically relevant non-major bleeding was 22.1%, 18.1%, and 13.4% for patients with a low, moderate, and high physical activity level, respectively ($P=0.01$ by the logrank test).

Panel C. Kaplan-Meier estimates of a first fall-related major or clinically relevant non-major bleeding by physical activity level

The 2-year cumulative incidence of a first fall-related bleeding was 9.9%, 3.9%, and 4.1% for patients with a low, moderate, and high physical activity level, respectively ($P<0.001$ by the logrank test).

Table 1. Patient baseline characteristics

Characteristic*	All (n=988)	Low physical activity level (n=367)	Moderate physical activity level (n=310)	High physical activity level (n=311)
n (%) or median (range)				
Age, years	75 (65-97)	78 (65-96)	76 (65-97)	71 (65-90)
Female gender	461 (47)	207 (56)	152 (49)	102 (33)
Overt pulmonary embolism	684 (69)	254 (69)	215 (69)	215 (69)
Unprovoked VTE [†]	598 (60.5)	195 (53.1)	196 (63.2)	207 (66.6)

History of major bleeding	101 (10)	51 (14)	25 (8)	25 (8)
Recent surgery	148 (15)	45 (12)	52 (17)	51 (16)
Cerebrovascular disease	92 (9)	45 (12)	33 (11)	14 (5)
Cardiac disease [†]	241 (24)	117 (32)	62 (20)	62 (20)
Diabetes mellitus	154 (16)	79 (22)	49 (16)	26 (8)
Arterial hypertension	636 (64)	272 (74)	200 (65)	164 (53)
Active cancer [§]	177 (18)	82 (22)	58 (19)	37 (12)
Chronic liver disease	14 (1)	7 (2)	4 (1)	3 (1)
Chronic renal disease	185 (19)	83 (23)	60 (19)	42 (14)
High risk of falls	457 (46)	248 (68)	135 (44)	74 (24)
Anemia [#]	386 (39)	175 (48)	124 (40)	87 (28)
Thrombocytopenia ^{**}	140 (14)	61 (17)	45 (15)	34 (11)
Polypharmacy ^{††}	503 (51)	249 (68)	154 (50)	100 (32)
Platelet inhibitors ^{††}	320 (32)	149 (41)	99 (32)	72 (23)

Characteristic	All (n=988)	Low physical activity level (n=367)	Moderate physical activity level (n=310)	High physical activity level (n=311)
	n (%) or median (range)			
Pre-existing VKA	58 (6)	27 (7)	18 (6)	13 (4)
Parenteral anticoagulation				
Low-molecular-weight heparin	467 (47)	158 (43)	147 (47)	162 (52)
Unfractionated heparin	329 (33)	137 (37)	98 (32)	94 (30)
Fondaparinux	158 (16)	58 (16)	50 (16)	50 (16)
No parenteral anticoagulation	34 (3)	14 (4)	15 (5)	5 (2)

Abbreviations: VTE= venous thromboembolism; VKA = vitamin K antagonist.

*Data were missing for history of major bleeding (0.1%), hemoglobin (6%), and platelets (6%).

[†] Any VTE unrelated to cancer or major surgery, immobilization, or estrogen therapy during the last 3 months

[‡]Acute heart failure during the last three months, a known history of systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, left ventricular ejection fraction <40%, a myocardial infarction with or without ST elevation during the last three months, or history of coronary heart disease.

[§]Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, and/or palliative care during the last three months.

^{||}Patients who answered “yes” to at least one of the following validated questions were considered at high risk of falls: 1) Did you fall during the last year? If not, then, 2) Did you notice any problems with gait, balance, or mobility (50)?

[#]Serum hemoglobin <130 g/l for men or <120 g/l for women.

^{**}Platelet count <150 G/l.

^{††}Pharmacotherapy with >4 different drugs.

^{‡‡}Use of aspirin, clopidogrel, prasugrel, or aspirin/dipyridamol.

Table 2. Incidence rates of a first bleeding by physical activity level

Bleeding type	Low physical activity level	Moderate physical activity level	High physical activity level
Major bleeding			
Incidence rate*	11.6 (9.1 - 14.8)	6.3 (4.5 - 8.8)	3.1 (2.0 - 4.8)
Number of events	65	34	19
Person-time, years	561	541	619
Clinically relevant non-major bleeding			
Incidence rate*	14.0 (11.2 - 17.6)	10.3 (7.9 - 13.5)	7.7 (5.7 - 10.3)
Number of events	76	53	45
Person-time, years	542	515	586
Fall-related bleeding			
Incidence rate*	6.1 (4.4 - 8.5)	1.9 (1.1 - 3.5)	2.1 (1.2 - 3.5)
Number of events	36	11	13
Person-time, years	589	565	631

* Events per 100 patient-years (95% confidence interval)

Table 3. Percentage of time in a given INR range by physical activity level

INR range*	All (n=784)	Low physical activity level (n=264)	Moderate physical activity level (n=257)	High physical activity level (n=263)	P- value
<2.0	25%	29%	26%	21%	<0.001
2.0-3.0	58%	55%	57%	63%	<0.001
>3.0	16%	17%	17%	15%	0.49

Abbreviation: INR = international normalized ratio.

*Only patients who received oral anticoagulation within 14 days from diagnosis were included in this analysis (N=830). INR values obtained during the first seven days of each treatment period were omitted. A total of 46 patients with incalculable time in a given INR range (no or only one INR measurement available) were excluded.

Table 4. Association between physical activity level and bleeding

Clinical characteristic	Adjusted SHR* (95% CI)
Major bleeding	
Physical activity level	
Low	1 (reference)
Moderate	0.72 (0.45 - 1.13)
High	0.40 (0.22 - 0.72)
Clinically relevant non-major bleeding	
Physical activity level	

Low	1 (reference)
Moderate	1.05 (0.73 - 1.51)
High	1.08 (0.69 - 1.67)

Abbreviation: SHR= sub-hazard ratio; CI= confidence interval.

*Multivariate competing risk regression model, accounting for death as a competing risk. The SHR is adjusted for age, gender, overt pulmonary embolism, history of major bleedings, recent surgery, cerebrovascular disease, cardiac disease, diabetes mellitus, hypertension, active cancer, chronic liver disease, chronic renal disease, high risk of falls (self-reported fall during the last year or existing problems with gait, balance, or mobility), anemia (hemoglobin <130 g/l for men or <120 g/l for women), thrombocytopenia (<150 G/l), polypharmacy, platelet inhibitor therapy, and periods of vitamin K antagonist treatment as time-varying covariate.

Figure 1. Patient flow chart







